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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,056	12/05/2003	David J. Grainger	295.009US4	9616

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
03/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/729,056	GRAINGER ET AL.	
	Examiner	**Art Unit**	
	UMAMAHESWARI RAMACHANDRAN	1617	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 11 March 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *153-155 and 157-173*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617

Note: Applicants' amendments (dated 3/11/2008) after final rejection will be entered. Applicants' arguments regarding the rejection of claims 153-155, 157-168 under 35 U.S.C. 112, first paragraph will be withdrawn due to the amendment of claim 153. Applicants' arguments regarding the 103 (a) rejections have been fully considered and found not to be persuasive. The claims are not allowable for the following reasons.

103(a) rejections, Sawada in view of Ellis et al.
Applicants' argue that based upon the disclosure of Sawada et al. it is unclear whether the reduction in total cholesterol is due to the action of toremifene on TGF- beta levels, whether it is due to the toxicity of torimifene or if it is due to the decrease in food consumption. In response, Sawada et al. teach a reduction of cholesterol upon administration of toremifene and the claims of the instant invention are directed to a method of treating a vascular indication and not towards a mechanism. That applicant may have determined a mechanism by which the active ingredient gives increasing the level of TGF-beta to decrease lesion formation or inhibition of lipid accumulation does not alter the fact that the compound has been previously used to obtain the same pharmacological effects (lowering total cholesterol) which would result from the claimed method upon the administration of same active agent in a same amount to the mammal in need thereof. An explanation of why that effect occurs does not make novel or even unobvious the treatment of the conditions encompassed by the claims. Also the appicants' argue that Sawada et al. teach away from the use of toremifene for noncancerous indications because tormifene administration may lower HDL-cholesterol. In response, Sawada et al. does not explicitly teach that tormifene administration may lower HDL-cholesterol. Hence it is not a teaching away from using toremifene for noncancerous indications.

103(a) rejections, Gylling et al. in view of Ellis et al.
Applicants' argue that Gylling et al. teach away from the use of agents such as tamoxifen and toremifene in nancancerous indications, due to the harmful effects of cholesterol synthesis observed with TMX and toremifene administration. In response, Gylling studies show that administration of TMX showed a gradual increase in delta-8 cholestenol and the increase appeared to be relatively small suggesting that harmful side effects related to this sterol may be few, if any, even possibly in long-term tamoxifen treatment (p 246, col.1, lines 12-15). Hence it is clear from the studies of Gylling teach the increase in cholestenol after tamoxifen administration and not toremifene and further teach that the increase appeared to be relatively small suggesting that harmful side effects related to this sterol may be few. The reference teaches that decrease in serum cholesterol upon administration of tamoxifen and inhibition of cholesterol synthesis with both tamoxifen and toremifene and a long-term use of tamoxifen as adjuvant therapy has revealed a cardioprotective effect (p 245, col. 1). Hence the teachings of Gylling do not teach away from using compounds like toremifene in
nancancerous indications.

103(a) rejections, Ito in view of Schilling
Applicants' argue that Ito et al. teach the use of toremifene in autoimmune diseases and combinations of Ito et al, Schilling, Knabbe or Kangas teach the instant invention. In response, Ito et al. in the background teach that toremifene is a remedy for autoimmune disease and include necrotizing angitis (inflammation of blood vessel) and granulomatous angitis as autoimmune diseases. Schilling teaches that angitis mainly affect small to average size arteries. Hence it would have been obvious to one of ordinary skill in the art at the time of the invention to have administered toremifene in a method of treating cardiovascular indication because Ito et al. teach toremifene is useful in the treatment of angitis (that affects small to average size arteries).

Applicants' argue that Warri et al. teaches away from the use of toremifene in non cancerous conditions. In response, Warri et al. is used to show that elevated TGF beta 1 mRNA was observed in vitro and in vivo grown tumor cells treated with toremifene.